IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit	: 1633	**Customer No.: 035811**
Examiner	: Maria Marvich	
Serial No.	: 10/764,628	
Filed	: January 26, 2004	
Inventors	: Véronique Trochon-Joseph	Docket No.: 1002-04
	: He Lu	
	: Claudine Soria	Confirmation No.: 9953
Title	: METHOD OF INHIBITING	
	: ANGIOGENESIS OR	
	: INVASION OR FORMATION	
	: OF METASTASES	

DECLARATION OF VÉRONIQUE TROCHON-JOSEPH UNDER RULE 132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir :

I, Véronique TROCHON-JOSEPH, residing at 33 rue du Génie, 94400 Vitry sur Seine (France), declare and say that:

I am citizen of France.

I have a PhD degree in Pharmacology and graduated from the Rouen University (France) in 1998.

Since 2001, I have been employed by BioAlliance Pharma Company as a Project Manager where I developed the anti-angiogenic and anti-invasive metargidin disintegrin peptide project.

I am one of the inventors named in the above-identified US patent application and I am thoroughly familiar with the subject-matter described and claimed therein.

I am aware that the Patent Office considers that the document Fanslow et al. (US Patent No. 7,074,408) would teach to use disintegrin domain of metargidin in treatment of cancer and vessel formation.

However, when I developed the anti-angiogenic and anti-invasive metargidin disintegrin peptide project, I anticipated that expression of a polypeptide consisting of the metargidin disintegrin domain alone would probably be jeopardized because of problems of instability.

Indeed, the disintegrin domain of metargidin contains 15 cysteine residues in positions 5, 16, 18, 24, 28, 29, 34, 42, 48, 49, 52, 61, 68, 74, and 81 of the 91 amino acid long domain.

It is well known in the art that pairings of cysteine residues in proteins occur by oxidation of their thiol groups and formation of disulfide bonds. Disulfide bonds play an important role in the folding and stability of proteins as disulfide bridges between cysteine residues within a polypeptide support the protein's tertiary structure.

Because of its odd number of cysteine residues, I anticipated that at least one of the cysteine residues of the disintegrin domain of metargidin would normally be implicated in a disulfide bond with another domain of the entire metargidin protein, thereby participating in the stabilisation of the disintegrin domain. In a context where the disintegrin domain of metargidin alone is expressed, it was thus assumed that the lack of this inter-domain disulfide bond – due to the absence of the other domain of metargidin implicated in the disulfide bond – would lead to instability of the disintegrin domain of metargidin.

More generally, all disintegrin domains of ADAM proteases contain an odd number of cysteine residues and it was thus a prevailing assumption in the art that they would be unstable when expressed alone.

Before the filing date of the above-identified patent application, when others undertook expressing the disintegrin domain of metargidin, e.g. for characterization of its interaction with integrins, they produced a chimeric polypeptide comprising the entire extracellular domain of metargidin (including the disintegrin domain) fused to the Fc portion of human IgG. This work was published by Nath et al. in the Journal of Cell Science (112, 579-587, (1999)), and Nath et al. expressly mentioned that a reason for the construction of this chimeric protein was that the disintegrin alone may

not be stable on its own (page 581, right-handed column, first paragraph under the heading "cell-chimeric adhesion assays for metargidin binding").

Upon reading the entire content of Fanslow et al. (US Patent No. 7,074,408), I would not have come to the conclusion that it was possible to express a stable polypeptide consisting of the disintegrin domain of metargidin only.

Fanslow et al. essentially disclosed that the ADAM disintegrin domain polypeptides are preferentially in multimeric form or in the form of fusion polypeptides. It is my understanding that such forms were preferentially contemplated by Fanslow et al. because they would be more stable than an ADAM disintegrin domain alone. This is actually evidenced by the fact that Fanslow et al. mentioned in column 9, in lines 19-21, that the oligomers of ADAM disintegrin domains can be linked by disulfide bonds formed by cysteine residues on different ADAM disintegrin domain polypeptides. It thus appears evident that multimerization was intended to stabilize ADAM disintegrin domains by establishing bridges between unpaired cysteine residues of the disintegrin domains.

Additionally, the ADAM disintegrin domain polypeptides described in the examples of Fanslow et al., in particular in example 1, all consist of chimeric proteins comprising not only ADAM disintegrin domain but also additional ADAM sequences fused to the Fc region of an immunoglobulin. The presence of additional ADAM sequences can be drawn form the size of the ADAM disintegrin sequence in the construct, e.g. amino acids 23 to 292 of the construct for ADAM-15dis-Fc disclosed in Table 2, whereas ADAM-15 disintegrin domain is "only" 91 amino acid long).

The overall disclosure of Fanslow et al. is exactly consistent with the disclosure of Nath et al. (*supra*) who produced a chimeric polypeptide comprising the entire extracellular domain of metargidin fused to the Fc portion of human IgG to circumvent instability of the disintegrin domain alone.

Therefore, I do not believe that Fanslow et al. would have taught or suggested using a polypeptide consisting of the disintegrin domain of metargidin in treatment of cancer and vessel formation.

The undersigned Declarant declares further that all statements made herein of her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed on May 9th, 2011

Véronique TROCHON-JOSEPH, co-inventor